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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/709,739	05/26/2004	Itzhak Bentwich	050992.0302.00USCP	3738

37808 7590 06/26/2009

ROSETTA-GENOMICS
c/o PSWS
700 W. 47TH STREET
SUITE 1000
KANSAS CITY, MO 64112

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
06/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/709,739	BENTWICH ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,31,33 and 35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,31,33 and 35-37* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2004 and 02 January 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/18/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/18/09 has been entered.

Claims 26, 31, 33, and 35-37 remain pending and under consideration.

Rejections and objections not reiterated are withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following rejection was previously withdrawn on 2/18/09 in view of Applicant's amendments and arguments. After further review and consideration of pertinent findings of the court, the rejection is reinstated.

Claims 31 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Ghazal et al (WO/200257437).

Ghazal taught a yeast artificial chromosome vector comprising nucleotides 163187-163253, which are identical to instant SEQ ID NO: 4204050, and which

comprise instant SEQ ID NO: 117937. Accordingly Ghazal taught a vector that comprised a sequence consisting of instant SEQ ID NO: 4204050, and a sequence consisting of instant SEQ ID NO: 117937. See abstract and alignment below.

```
Qy          1 GACAGCCTCCGGATCACATGGTTACTCAGCGTCTGCCAGCCTAAGTGACGGTGAGATCCA 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     163187 GACAGCCTCCGGATCACATGGTTACTCAGCGTCTGCCAGCCTAAGTGACGGTGAGATCCA 163246

Qy         61 GGCTGTC 67
              |||||||
Db     163247 GGCTGTC 163253
```

'Qy' refers to instant SEQ ID NO: 4204050, and 'Db' refers to the sequence of Ghazal.

This rejection has been reinstated after a review of the findings of the court in *In re* Crish, 73 USPQ2d 1364 (Fed. Cir. 2004). In that decision the court found that claims drawn to a purified oligonucleotide comprising a portion of SEQ ID NO:1, wherein said portion consists of the nucleotide sequence from 521 to 2473 of SEQ ID NO: 1, were anticipated by the prior art disclosure of a nucleotide sequence comprising SEQ ID NO: 1. The court affirmed the Board's claim construction, finding that a "reasonable interpretation of the claims containing both of the terms "comprising" and "consists" is that the term "consists" limits the "said portion" language to the subsequently recited numbered nucleotides, but the earlier term "comprising" means that the claim can include that portion plus other nucleotides. [Footnote omitted] Read in context, the claims thus do not preclude a DNA sequence having additional nucleotides." This situation is analogous to the instant situation in which the claims are drawn to a vector comprising a heterologous sequence, wherein the heterologous sequence is selected

from the group consisting of SEQ ID NO: 4204050 or 117937, etc. The instant claims have essentially the same construction as those in *Crish*, being drawn to a nucleic acid (vector) comprising a heterologous sequence, wherein the heterologous sequence consists of a specified SEQ ID. The instant claims do not preclude the presence in the vector of CMV sequences other than SEQ ID NOS: 4204050 or 117937. Therefore Ghazal anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 26 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ghazal et al (WO/200257437) in view of Hogan (US Pat. 5,541,308, July 30, 1996).

Ghazal taught a yeast artificial chromosome vector comprising at least a portion of a human cytomegalovirus genome, wherein the portion includes nucleotides 163187-163253, which are identical to instant SEQ ID NO: 4204050. Accordingly Ghazal taught a vector that comprised a sequence consisting of instant SEQ ID NO: 4204050.

Ghazal did not teach an isolated nucleic acid consisting of SEQ ID NO: 4204050, or a probe comprising SEQ ID NO: 4204050.

However the complete sequence of the vector insert of Ghazal comprising SEQ ID NO: 4204050 was known in the prior art at the time the invention was made. Further, the parameters and objectives for generating probes were well known in the art at the time the invention was made. For example, Hogan taught methods for generating target specific primers (col. 6-7, lines 50-67, lines 1-12), and provides extensive guidance for the selection of primers and probes. Hogan taught that "while oligonucleotide probes of different lengths and base composition may be used, oligonucleotide probes preferred in this invention are between about 15 and about 50 bases in length" (column 10, lines 13-15). Accordingly it would have been obvious to one of ordinary skill in the art at the time of the invention to generate a probe of any length corresponding to any fragment of the CMV genome, including the portion identical to SEQ ID NO: 4204050 disclosed by Ghazal.

Claims 35 and 37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ghazal et al (WO/200257437) in view of Buck et al (BioTechniques 27: 528-536, 1999).

Ghazal taught a yeast artificial chromosome vector comprising at least a portion of a human cytomegalovirus genome, wherein the portion includes nucleotides 163187-163253, which are identical to instant SEQ ID NO: 4204050, and which comprise instant SEQ ID NO: 117937. Accordingly Ghazal taught a vector that comprised a sequence consisting of instant SEQ ID NO: 4204050, and that comprised a sequence consisting of instant SEQ ID NO: 117937.

Ghazal did not teach an isolated nucleic acid consisting of SEQ ID NO: 117937, or a probe comprising SEQ ID NO: 117937. However, it is clear that it was obvious to those of ordinary skill in the art that sequencing primers were required in order to obtain the sequence disclosed in Ghazal, and it was of interest to amplify subsequences along the entire length of the sequence of Ghazal (see e.g. Table 1 of Ghazal). It is considered obvious for the reasons set forth below to make primers of the same length of SEQ ID NO: 117937, and further, these primers can be considered to be probes.

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all

possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

It would have been obvious to one of ordinary skill in the art at the time of the invention to synthesize instant SEQ ID NO: 117937 as a primer in the process of determining the sequence disclosed in Ghazal. In view of the teachings of Buck, sequencing primers can be synthesized essentially anywhere along a given sequence of interest, and under optimal conditions they will reasonably be expected to perform adequately to yield sequence data. See page 533, left column, first full paragraph, and paragraph bridging pages 535 and 536. It would have been obvious to select a primer length of 22 nucleotides because those of ordinary skill normally use sequencing primers of 19-24 nucleotides in length (see Buck abstract.). Accordingly, any 22 nucleotide fragment represented in either strand of the vector of Ghazal is considered to be obvious.

Response to Arguments

Applicant's arguments filed 4/18/09 have been fully considered but they are not persuasive.

Applicant states that Murphy et al (Proc. Nat. Acad. Sci USA 105: 5453-5458, 2008) "confirms the teachings of the specification that the IE-1 gene of HCMV is regulated in trans by the claimed miR (miR-UL12-1) (SEQ ID NO: 117937)." Applicant concludes that this is evidence of a secondary consideration that the claimed miR unexpectedly regulates a gene in trans and is therefore distinguishable and unique

amongst the 8,255,610 or 1,834,676 possible probes or primers that could be arrived at based on the teachings of Ghazal in view of Hogan and Buck, respectively.

As a preliminary matter, it is noted that the miRNA of Murphy is not identical to SEQ ID NO: 117937. Although it is comprised within SEQ ID NO: 4204050, it is offset by one nucleotide within that sequence when compared with instant SEQ ID NO: 117937. A comparison of SEQ ID NO: 117937 and miR-UL12-1 is given below:

```
SEQ ID NO: 117937     1 AGUGACGGUGAGAUCCAGGCUG 22
                        ||||||||||||||||||||
   miR-UL12-1         1 AAGUGACGGUGAGAUCCAGGCU 22
```

Applicant's arguments are unpersuasive because the unexpected finding relied upon by Applicant as evidence of a secondary consideration to overcome the obviousness rejection is not envisioned in the specification and does not flow from the teachings of the functions and advantages disclosed in the specification as filed. In other words, Murphy does not provide evidence supporting any feature disclosed in the specification that could be seen as a secondary consideration mitigating the obviousness rejection. It is the position of the Office that the discovery after the time of the invention of a use for the claimed product, that is different from any use disclosed in the specification, does not constitute a secondary consideration persuasive of non-obviousness.

The specification as filed indicates that SEQ ID NOS: 117937 and 4204050 comprise an miRNA, and appears to disclose 4 targets of the miRNA. These targets include a human mRNA encoding surfactant protein A1 (SFTPA1), and three sites

encoded in the CMV genome: one in the UL43 gene, which gene occupies the complement of CMV nucleotides 54824-56095; one in the IRS1 gene, which gene occupies CMV nucleotides 190696-193236; and one in the US1 gene, which gene occupies the complement of CMV nucleotides 193237-193637. The specification discloses that the miRNA down-regulates these targets. The CMV IE-1 gene disclosed by Murphy occupies the complement of CMV nucleotides 171937-173696, and so is not one of the targets disclosed in the instant specification. Murphy also predicts that miR-UL12-1 may target CMV genes UL31 and UL34, but these genes are not disclosed as targets of SEQ ID NO: 117937 by the instant specification. Murphy does not disclose UL43, IRS1, or US1 as targets of miR-UL12-1. See Table 1. Accordingly, the evidence of the Murphy cannot be said to confirm the teachings of the specification, because the specification does not teach that any one of the IE-1, UL31, or UL34 genes of HCMV is regulated in trans by the claimed miR, and Murphy does not disclose that miR-UL12-1 targets SFTPA1, UL43, IRS1, or US1.

In summary, Murphy confirms the assertion in the specification that SEQ ID NO: 4204050 comprises the sequence of an miRNA, but does not confirm the uses set forth in the specification for that miRNA. Thus Murphy does not provide evidence that the uses envisioned by the specification, either as an miRNA to down regulate SFTPA1, UL43, IRS1, or US1, or as a probe of an miRNA with at least one of those functions, are enabled. The use as a probe for detecting or sequencing HCMV is enabled, but is considered obvious for the reasons set forth above in the rejections. Murphy provides evidence of an unexpected property relative to the obviousness rejection, i.e. miR-

UL12-1 down regulates IE-1 in infected cells. However, this unexpected property is not envisioned in the instant specification, and does not flow from the teachings of the functions and advantages disclosed in the specification as filed, and so is not considered persuasive as a secondary consideration of non-obviousness. Applicant disclosed a nucleic acid that could be processed to miR-UL12-1 (SEQ ID NO: 4204050) but did not teach that it could be used for the purpose that Murphy discloses. The fact that Murphy discovered a separate, distinct, undisclosed use for the claimed nucleic acid does not provide evidence of the non-obviousness of Applicant's claimed invention because Applicant did not invent what Murphy discovered. For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635